December 20, 2002

Kenneth P. Morgan
Manager, Technical Support Services
Merisol USA LLC
1914 Haden Road
Houston, Texas 77015-6498

Dear Mr. Morgan:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Mixed Xylenol Category posted on the ChemRTK HPV Challenge Program Web site on August 16, 2002. I commend the Merisol USA LLC for its commitment to the HPV Challenge Program.

EPA also must bring to your attention the fact that the acute toxicity test which you have proposed is specifically not recommended for use in the HPV Challenge Program (65 FR 81695) where the recommended guideline is OECD TG 425 (the "Up and Down Method"). In addition, the Organization for Economic Cooperation and Development (OECD) has made the decision to remove OECD TG 401, and test data using the guideline generated after December 20, 2002 need not be accepted by other OECD countries under Mutual Acceptance of Data. Note, also, that EPA encourages Challenge sponsors that have proposed acute toxicity testing to use an in vitro dose range-finding protocol to set the starting dose for the Up and Down test. Information on this protocol is available at http://www.epa.gov/chemrtk/toxprtcl.htm. Finally, EPA recommends an in vitro chromosomal aberration study instead of the in vivo micronucleus (OECD 474) proposed.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Merisol advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
W. Penberthy
A. Abramson
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission: Mixed Xylenols

SUMMARY OF EPA COMMENTS

The sponsor, Merisol USA LLC, submitted a test plan and robust summaries to EPA for the mixed xylenols category dated July 29, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 16, 2002. The category consists of six xylenol isomers.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. EPA believes the submitter should use available data on the xylenol isomers rather than rely solely on the submitted cresol data (especially for health

effects). Furthermore, the submitter should consider testing a xylenol isomer mixture that more closely resembles a Merisol product that either (a) is sold in the highest production volume, or (b) has the highest percentage of xylenol isomers.

3. Physicochemical Properties and Environmental Fate. EPA believes the submitted physicochemical and biodegradation data on the six individual xylenol isomers are likely sufficient for the purposes of the HPV Challenge Program. However, adequate robust summaries need to be submitted. EPA further believes that (a) hydrolysis testing is not necessary; (b) there should be a discussion about possible direct photodegradation; and (c) fugacity modeling is not appropriate for mixtures. Because the submitted physicochemical properties data show similar values for all isomers, testing of a mixture would not add any new information and thus may not be necessary.

4. Health Effects. EPA questions the proposed approach on two grounds: (1) use of the cresols data for xylenols may not be appropriate because cresols involve only one substituent on a phenol and the xylenols have two substituents; and (2) the available xylenol isomer data show toxicity differences among the xylenol isomers. Therefore, EPA believes the submitter should not test an equimolar mixture of xylenol isomers. Instead, the submitter may want to consider performing health effects testing on a Merisol product as stated above under Category Justification. Adequate robust summaries need to be submitted for all the xylenol data.

5. Ecological Effects. EPA believes that testing any of these xylenols as a mixture or individually would produce similar results and would not add meaningful information. For this reason, EPA believes that the submitted existing fish and invertebrate data, plus fish data identified by EPA (see below) not cited in the test plan on several of the xylenols show that fish and invertebrates endpoints have been met for the purposes of the HPV Challenge Program. For the algal endpoint, data exist for only 2,6-xylenol, and EPA is reserving judgment until an adequate robust summary is submitted for that study to determine whether more testing is needed for this endpoint. Adequate robust summaries need to be submitted for all the xylenol data.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE MIXED XYLENOLS CHALLENGE SUBMISSION

General

This submission is similar to the Ethylphenols Category submission from the same sponsor. In reviewing both submissions, it appears that most of the submitter's commercial products are mixtures of xylenols, phenols, cresols, and ethylphenols. According to the Merisol Web site (www.merisol.com), the following xylenol products are available for sale: 2,4/2,5 xylenol mixture; "mixed xylenols and ethylphenols"; high purity xylenols (pure 3,4-isomer listed as what is currently available); and "blended cresylic acid products" (what appears to be the starting Merisol fraction used to develop the cresols, xylenols, and ethylphenols).

Table 1 in the test plan states that only 27.5% of the Merisol products contain all six xylenol isomers, but provides no information on the percentage composition range for xylenols, phenols, cresols, and ethylphenols in those products. The submitter needs to provide specific information on: (1) whether any commercial products consist of single xylenol isomers (e.g., the 3,4-xylenol identified on the Merisol website), and (2) the percentages of the xylenol isomers in typical commercial products, with a description of the rest of the product composition.

Category Definition

The submitter proposes a category of individual xylenol (dimethylphenol) isomers and mixtures of xylenol isomers. The xylenol isomers are: 2,3-xylenol (CAS No. 526-75-0); 2,4-xylenol (CAS No. 105-67-9); 2,5-xylenol (CAS No. 95-87-4); 2,6-xylenol (CAS No. 576-26-1); 3,4-xylenol (CAS No. 95-65-8); and 3,5-xylenol (CAS No. 108-68-9), along with mixed xylenols (CAS No. 1300-71-6). The submitter notes that "mixed xylenols" is not compositionally defined by EPA or industry and a number of products can be so identified. The submitter also notes that commercial xylenol products are primarily composed of two or more xylenol isomers, except for one substance that contains predominantly 2,6-xylenol. In addition, those commercial products containing xylenol also contain other phenolics including phenol, cresols, and ethylphenols. No information is provided in the test plan that identified the amounts of other components of commercial xylenol mixtures (see above under General).

Category Justification

The submitter bases the category on the close structural relationship of the xylenol isomers, the similar physicochemical and environmental fate properties observed across the six isomers (Table 3 in the test plan), and the anticipated similarities for ecological effects and health effects. The submitter further states that the six xylenol isomers should be considered similar from a health effects standpoint on the basis of data from isomers of cresol (*o*-cresol, *m*-cresol, *p*-cresol, and an *m/p*-cresol mixture).

The submitter provided physicochemical and environmental fate data for all six xylenol isomers showing that these properties of the xylenol isomers are similar. Therefore, the physicochemical and environmental data support the category.

The toxicological justification for treating the six xylenol isomers as a category is based on results of toxicity studies performed with a group of "structurally related compounds," the three cresol isomers (o, m, and p). The submitter stated that the cresol isomers are "remarkably equivalent in toxicity," and further indicated that similarities in toxicity among the individual cresol isomers and binary and tertiary cresol mixtures result from structural similarities between the individual cresol isomers. The submitter argued that this "demonstration of a structure-activity relationship" among the cresol isomers provides the toxicological justification for a similar structure-activity relationship among the xylenol isomers. A number of issues in the presented information need to be addressed by the submitter.

The submitter stated that National Toxicology Program (NTP) studies of cresols indicated that target organs and toxic effect dose levels were relatively consistent across the isomers. The referenced NTP studies were oral repeated-dose studies in which toxicities of the individual cresol isomers and a mixture of *m* ! and *p* ! cresol (60/40) were similar. The submitter stated that the author of the NTP studies concluded that the cresol isomers exhibited similar toxicities with "few exceptions." However, the submitter did not characterize these "exceptions". EPA identified the NTP summary online (http://ntp-server.niehs.nih.gov/ - click on search and type "cresol," click on "TOX-9" report). The exceptions are noted there. Similarities noted were increases in liver and kidney weights, and bone marrow hypoplasia and uterus, ovary and mammary gland atrophy (these latter effects were seen at different doses) in all rats exposed to all cresols. Specific effects were seen only in rats exposed to *p*-cresol or *m/p*-cresol (atrophy and regenerative changes in the nasal epithelia and forestomach), and *o*-cresol and *m/p*-cresol (lengthened estrus cycles).

The rabbit and rat developmental toxicity studies of the cresol isomers (unpublished reports from Bushy Run Research Center), provided by the submitter as evidence for similarity of toxicity among cresol isomers and summarized in the submitter's Attachment I, were critically reviewed by EPA as part of evaluating data submitted pursuant to a TSCA section 4 rule. EPA concluded that generally similar results were obtained for each of the cresol isomers, although maternal and fetal toxicity in rats appeared to be slightly greater for *p*-cresol than for *m*- or *o*-cresol.

EPA believes that the cresol data are less relevant to dialkyl phenols than to monoalkyl phenols because of the increased number of possible isomers and of the possible resulting effects on pharmacokinetics and toxicity. The submitted xylenol isomer data submitted support this concern.

EPA believes the available data on the xylenol isomers should be used to determine whether the xylenols may behave similarly to each other as appears to be the case for the cresols. For example, acute mammalian toxicity data in Table 4 for five of the six xylenol isomers suggests that the 2,6-isomer is 4-9 times more toxic than any other isomer. The only two repeated-dose toxicity data points (2,4- and 2,6- isomers) suggest a possible 100-fold difference in toxicity. However, the necessary analysis is hampered by the lack of appropriate robust summaries for all the xylenol data (Appendix E in the test plan).

The data provided for the acute fish and invertebrate toxicities, along with the EPA data cited below, suggest a pattern for the toxicities of the category members and support the submitter's conclusion of similar toxicities for these two endpoints.

Test Plan

The submitter states that the properties of xylenols mixtures will not vary significantly with changes in the proportion of the individual xylenol isomers in the mixtures. Therefore, because the commercial products containing xylenols exist predominantly as mixtures, the submitter proposes to use an equimolar mixture of all six xylenol isomers as a representative substance for the mixed xylenol category. EPA understands the logic behind this plan, but believes the submitter should consider conducting the SIDS-level tests with a commercial product containing all six isomers.

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

EPA believes the submitted data on the physicochemical properties are sufficient for addressing these endpoints for the purposes of the HPV Challenge Program. Testing of an equimolar mixture is not necessary. However, if the purpose of testing the mixture is to enhance the toxicity test design, then such testing is reasonable.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

For photodegradation, no additional estimation is necessary, however, the mixed xylenol isomers may be susceptible to direct photolysis and a technical discussion explaining the relative importance of this fate pathway should be provided. EPA believes that hydrolysis testing is not appropriate for these substances. The submitted biodegradation data on the individual isomers may be sufficient, but EPA reserves judgment until adequate robust summaries are submitted. Finally, the fugacity endpoint, which is fulfilled by modeling, may not be run appropriately with mixtures.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Results of available health effects studies for each of the six individual xylenol isomers were summarized in the test plan, but most of the corresponding robust summaries were incomplete. Although the test plan stated that similarities in results of existing mammalian health effects studies for individual xylenol isomers support the treatment of xylenols as a category, it acknowledged the paucity of comparative information and noted that some of the available data may not be useful due to inadequate reporting of study details. The submitter argued that toxicological responses to a group of related chemicals, the methylphenols (cresols), are similar among individual cresol isomers. The submitter stated that similarity of toxicological responses would also be expected among the six individual xylenol isomers. Therefore, the submitter proposed that an equimolar mixture of the six xylenols be used to assess the potential hazards of exposure to xylenol-containing substances, the results of which would be applicable to all mixtures of xylenols and to each of the six individual isomers. Testing would include acute mammalian toxicity, a combined repeated-dose reproductive/developmental toxicity screen, and genetic toxicity (assays for bacterial mutagenicity and mammalian erythrocyte micronuclei). Tests would be developed according to OECD guidelines.

EPA notes that the existing xylenol data show differences among the isomers that could be important: (1) the acute toxicity range of 296 to 2300 mg/kg/d, and (2) the difference in response to repeated-dose exposures (three-month study with the 2,4-isomer resulted in a NOAEL of 50 mg/kg/d showed nervous system toxicity and reported no other organ toxicity while the eight-month study with the 2,6-isomer reported an 0.6 mg/kg/d NOAEL with effects on the kidney, liver, and spleen). The repeated-dose studies suggest both potency and target organ effect differences. Importantly, these reflect the least and most toxic isomers, respectively.

The submitter's proposal of testing an equimolar mixture assumes that each component of the mixture contributes equally to the effect being measured. This does not appear to be the case for the xylenol isomers. In fact, the NTP studies with the cresol mixture (a 60:40 mixtures of *m*-and *p*- isomers) were not equimolar.

The submitter stated that more than 60% of the available xylenol products have five or six xylenol isomers. Details on the relative amounts of xylenol isomers in specific mixtures were not presented.

The submitter needs to consider the possibility that significant differences in toxicity among the various xylenol isomers could result in inaccurate toxicological assessments if health effects tests are performed using only an equimolar mixture of the six xylenol isomers. Although there are inherent uncertainties related to selection of any mixture to represent the toxicity of all xylenols isomers and commercial mixtures, it is important to select a mixture with a composition that reflects the potential for exposure. The submitter

needs to test a commercially available composition of xylenols representative of xylenol mixtures that would be most likely to contribute to significant human exposure.

Ecological Effects (fish, invertebrates, and algae).

Fish and Invertebrates. The data submitted were not in robust summary format, they were in good agreement with data cited in EPA databases and those from structure-activity relationships using the EPIWIN model. EPA found additional fish data for 3,4-xylenol (Matson, 1976), 2,4-xylenol (Geiger, 1985), and 2,6-xylenol (OECD, 1997) not cited in the test plan. EPA suggests that the submitter provide robust summaries for the key studies.

Algae. EPA reserves judgment on this endpoint pending receipt of an adequate robust summary for the existing algal study performed with the 2,6-isomer.

The submitter's proposal to conduct acute fish, invertebrate, and algal toxicity testing on a mixture containing equal portions of the xylenols is not critical for ecological effect endpoints. EPA believes the xylenol isomers have similar aquatic toxicities and the available information should be used accordingly.

Specific Comments on the Robust Summaries

Generic comments

Appendices A-D, while useful, contained robust summaries that pertain only to cresol data, most of which describe studies reviewed as part of the TSCA Section 4 action mentioned above. Appendix E (pp. 59-66) was the only information on available xylenol isomer data. There were no robust summaries submitted for any of the xylenol isomer data for physicochemical properties or environmental fate endpoints. This information is necessary to meet the obligations of the HPV Challenge Program.

Health Effects

All of the health effect robust summaries in Appendix E lack sufficient detail to assess the adequacy of the underlying data. This includes the studies identified as "valid without restrictions". The submitter is encouraged to review the guidance on developing robust summaries and consider revising all the robust summaries (available at: http://www.epa.gov/chemrtk/robsumgd.htm).

Ecological Effects

EPA considers the submitted fish data for 2,4-xylenol, 2,5-xylenol, and invertebrate data for 2,3-xylenol, 2,5-xylenol, and 2,6-xylenol adequate, pending submission of the robust summaries providing critical data elements including pH, water temperature, water hardness, dissolved oxygen, and chemical purity.

Fish. Appendix E of the submission contained summaries of five acute fish toxicity studies on 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-xylenol. The summaries reported no information beyond the LC50 value, test type (static vs. flow-through), species tested, and study year. Because of these deficiencies, adequacy of the data could not be fully evaluated.

Invertebrates. Appendix E of the submission contained summaries of three acute invertebrate toxicity studies on 2,3-, 2,5-, and 2,6-xylenol. The summaries reported no information beyond the LC50 value, test type, species tested, and study year. Because of these deficiencies, adequacy of the data could not be fully evaluated.

Algae. Appendix E of the submission contained a summary of one aquatic plant toxicity study on 2,6-xylenol. The summary reported no information beyond the LC100 value, test type, species tested, and study year. Because of these deficiencies, adequacy of the data could not be fully evaluated.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

Inconsistencies and Typographical Errors

On page 6 (Table 3), the submitter reported a melting point of 25^{o}C for 2,3-xylenol. This is likely a typographical error because EPA located several values in the literature that range from 72.6 to 75^{o}C.

On page 8 (a. Mammalian Acute and Repeated Dose Toxicity), the submitter stated that acute oral LD_{50} values were 1470 and 1750 mg/kg for 2,6-xylenol in rats; however, Table 4 and the robust summary (p. 62) lists a value of 296 mg/kg for this isomer.

On page 8 (a. Mammalian Acute and Repeated Dose Toxicity), the submitter inadvertently reported a NOAEL of 0.06 mg/kg/day from a 10-month repeat oral dose toxicity study in rats administered 2,6-xylenol. The NOAEL is listed as 0.6 mg/kg/day in Table 4 and in the robust summary (p. 62).

On page 8 (a. Mammalian Acute and Repeated Dose Toxicity), the submitter cited a Russian report of a rat 90-day repeat oral dosing study for 2,4-xylenol in which a NOAEL of 50 mg/kg/day was reported. However, the only submitted robust summary for repeat oral dosing of 2,4-xylenol was an unpublished US EPA 90-day repeat oral toxicity study that was performed on mice, not rats. The submitter needs to examine the source of the reported NOAEL and adjust the statement on page 8 accordingly. If indeed, both rat and mouse repeat oral dosing studies exist, a robust summary should also be submitted for the rat study.

On page 8 (c. Genetic Toxicity), the submitter states there are no bacterial mutation testing on the 2,3-isomer, but Table 4 (page 9) shows this gap is associated with the 3,5-xylenol.

On page 8 (c. Genetic Toxicity), the submitter stated that the xylenols have been tested for bacterial mutations using "several (but not five) Salmonella strains". However, robust summaries were submitted for only two strains (TA98 and TA100). The statement should be revised to indicate that only two strains were tested, not "several".

References

Geiger, D.L., et. al. 1985. "Acute Toxicities of Organic Chemicals to Fathead Minnows *(Pimephales promelas)*," Volume II, Center for Lake Superior Environmental Studies, University of Wisconsin-Superior, US EPA Cooperative Agreements, Superior, Wisconsin.

Matson, V.R., et. al. 1976. "Acute Toxicity of Selected Organic Compounds to Fathead Minnows," Ecological Research Service, US EPA-600/3-76-097, Environmental Research Laboratory, US EPA, Duluth, Minnesota.

OECD SIDS Dossier (1997). Draft dossier on 2,6-dimethylphenol submitted to EPA by GE Plastics (dated 2 September 1997).